PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Michael J. Breslin, *et. al*		
Serial No.:	10/506,702	Case No. 21047YP	Art Unit: 1626
Filed:	September 07, 2004		
For:	MITOTIC KINESIN INHIBITORS		Examiner: R. Havlin

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF CHRISTOPHER D. COX, PhD

Sir:

I Christopher D. Cox, PhD.,

do hereby declare that

1. I am employed by Merck & Co., Inc as a Senior Research Fellow in the department of Medicinal Chemistry. My *curriculum vitae* is attached as Exhibit 1.

2. My responsibilities at Merck & Co., Inc. include basic oncology research. I worked extensively on the discovery of mitotic kinesin inhibitors. During the course of that work, my team and I discovered many mitotic kinesin inhibitors, including those claimed in the instant application.

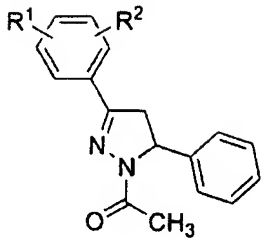
3. The compounds of the instant invention are 2,5-difluoro substituted 4,5-dihydro pyrazoles. The 2,5 difluoro substitution on the 3-phenyl unexpectedly results in a

favorable profile when compared to mono-fluorinated and other di-fluorinated analogues. The 2,5-difluoro compounds are very potent inhibitors of kinesin spindle protein (hereinafter "KSP").

The original HTS lead we discovered from screening our sample collection identified compound **A** with a 2-chloro substituent as a promising lead. We walked the chlorine to the 3- and 4-positions and noted a moderate loss in potency for the 3-position and a dramatic loss for the 4-position (compounds **B** and **C**). We interpreted the data to mean that 2- and 3-substitution were best, and 4-susbtitution was poor. We then changed the 2-Cl to a 2-F (compound **D**) and noticed similar potency, but since fluorine is less greasy and more compatible with optimal drug properties, we focused on fluoro substitution for our remaining analogues. Holding the fluorine in the 2-position constant, we added fluorines at the other positions that were optimal, specifically the 3-, 5- and 6 positions (note: by 3-, 4-, and 6-, I am assuming that the ring can rotate within our reference frame such that 2-subsitiution is the same as 6-substitution, 3- is the same as 5-, etc., but they are numbered differently when there is more than one substituent on the ring). What we noticed, quite unexpectedly, was that the 2,5-disubustitution yielded the most potent compound, indicating that in our original SAR study, it really was not the "3-position" that was good, but rather the "5-position" (compare compounds **E** and **G**). The.3,4-difluoro compound **H** was never made based on the lack of potency in compound **C** – I would expect this compound to have a potency of > 10,000 nM.

Table 1 summarizes the data described above:

Table 1.



Compound	R^1	R^2	ATPase (nM)
A	2-Cl	H	3,900
B	3-Cl	H	9,800
C	4-Cl	H	> 50,000
D	2-F	H	3,600
E	2-F	3-F	12,700
F	2-F	6-F	10,900
G	2-F	5-F	94
H	3-F	4-F	not made

4. These results were unexpected, and said results were realized prior to the filing date of the above-captioned application.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 or Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Christopher D. Cox, PhD

27-May-2009

Date